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Single Case

ANCA-Associated Glomerulonephritis and Anti-Phospholipid Syndrome in a Patient with SARS-CoV-2 Infection: Just a Coincidence?

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Antineutrophil cytoplasmic antibody-associated vasculitis · Antiphospholipid syndrome · COVID-19 · Rituximab

Abstract
Many reports have described a high incidence of acute kidney injury (AKI) among patients with COVID-19. Acute tubular necrosis has been reported to be the most common damage in these patients, probably due to hemodynamic instability. However, other complex processes may be involved, related to the cytokine storm and the activation of innate and adaptive immunity. Here, we describe a patient who developed an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis with rapidly progressive glomerulonephritis and lung involvement and an antiphospholipid syndrome soon after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. After viral pneumonia was excluded by bronchoalveolar

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lavage, the patient has been treated with rituximab for amelioration of kidney function and resolution of thrombosis without any adverse event. We conclude that COVID-19 may trigger autoimmune diseases including ANCA-associated vasculitis. Thus, this diagnosis should be taken in consideration in COVID-19 patients, especially when they develop AKI with active urinary sediment. In addition, considering the relationship between these 2 diseases, SARS-CoV-2 infection should be excluded in all patients with a new diagnosis ANCA-associated vasculitis before starting immunosuppressive therapy.

Introduction

Since March 2020, the infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is declared pandemic, and many reports have been published by scientific community in order to share clinical experience and to gain more information about this novel disease. The COVID-19 may have a very different course in the individuals, ranging from asymptomatic or mild form to a life-threatening systemic disease, with acute respiratory distress syndrome and multi-organ failure triggered by a cytokine release syndrome [1]. Several reports have described acute kidney injury (AKI) in patients with SARS-CoV-2 [2, 3]. Specifically, acute tubular injury represents the most common kidney damage found either on autopsies and kidney biopsies [4–6]. However, cases of collapsing glomerulopathy and thrombotic microangiopathy have also been reported [6, 7], while crescentic glomerulonephritis is still anecdotic [8, 9]. Moreover, many reports showed the association between SARS-CoV-2 infection and the antiphospholipid antibody detection, which may favor the prothrombotic state often experienced by these patients [10]. Here, we report a case of a patient who developed an antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis together with an antiphospholipid syndrome soon after SARS-CoV-2 infection.

Case Presentation

On May 2020, a 64-year-old woman with a medical history of hypertension, normal kidney function, and an episode of bacterial pneumonia in 2019, was admitted to the emergency room of the Urbino Hospital because of the onset of dyspnea and cough, refractory to antibiotic and steroid therapies. At admission, she was afebrile and her peripheral capillary oxygen saturation was 98% on air room. A chest computed tomography showed bilateral interstitial pneumonia with ground-glass opacities involving about 25% of pulmonary parenchyma. The real-time reverse transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2 on nasal and oropharyngeal swabs was negative. However, due to the strong epidemiological and radiological suspicion of SARS-CoV-2, she underwent an SARS-CoV-2 serological test that resulted positive for SARS-CoV-2 IgG Alifax (22.70 index) and for SARS-CoV-2 IgM (2.47 index). At admission, in Urbino Hospital, her serum creatinine was 1.8 mg/dL and the urinary sediment showed 20–200 erythrocytes per count ×400 together with proteinuria 50 mg/dL in the chemical analysis of the urine. Laboratory tests revealed proteinase-3-ANCA (PR3-ANCA) positive (761 U/mL at FEIA determination), while antinuclear and anti-double-stranded DNA antibodies tested negative. Thus, she was transferred to the unit of emerging and immunosuppressed infectious diseases at our hospital and few days after, to our nephrology, dialysis and renal transplantation unit. At admission to our unit, serum creatinine had

increased to 4.8 mg/dL, proteinuria was 3.3 g/day, and the presence of erythrocytes in the urinary sediment was confirmed. The complement fractions C3 and C4 were normal, C-reactive protein was elevated (9.4 mg/dL), and fibrinogen (886 mg/dL), D-dimer (2,145 ng/mL), and IL-6 (40.2 pg/mL). White blood cells were 11.240/mmc, hemoglobin 8.7 g/dL, and platelet count 288.000/mmc. Procalcitonin was slightly increased 0.74 ng/mL; IgG, IgA, and IgM were normal; and no monoclonal component was present in the serum protein electrophoresis. A nasopharyngeal scrub test for *Staphylococcus aureus* resulted negative.

A kidney biopsy was performed. Light microscopy showed glomeruli with cellular crescents, some of these with segmental fibrinoid necrosis and areas of sclerosis. Tubulitis and acute tubular injury were also present (Fig. 1a–d). An immunohistochemical stain panel for the interstitial inflammatory infiltrate showed the presence of mixed and not specific mononuclear cells (T and B lymphocytes, plasma cells, and macrophages) (Fig. 2). The glomeruli immunofluorescence studies were negative. The final diagnosis was pauci-immune glomerulonephritis.

On ultrastructural examination, no viral particles were found. RT-PCR for SARS-CoV-2 RNA performed on frozen renal tissue was also negative. The patient was immediately treated with pulsed dose steroids 3 doses together with plasma-exchange sessions. Meanwhile, intermittent hemodialysis by a central venous catheter placed in the right internal jugular vein was started due to further deterioration of kidney function. On day 10 from the hospitalization of the patient, a repeat oropharyngeal swab for SARS-CoV-2 tested again negative. However, due to the presence of SARS-CoV-2 IgG and IgM, we decided to perform a bronchoalveolar lavage in order to better characterize the etiology of the lung involvement and specifically to exclude COVID-19 infection, before starting the treatment with cyclophosphamide. The BAL excluded alveolar hemorrhage and was negative for SARS-CoV-2 RNA. Thus, cyclophosphamide was started. On day 15, the patient developed severe thrombocytopenia with the need to stop cyclophosphamide. The color-Doppler venous ultrasound revealed a massive thrombosis of the right jugular, brachiocephalic, and right subclavian veins, which was associated to elevated anticardiolipin IgM and anti-β2-glycoprotein I IgM (26.4 MPL/mL and 66.8 UA/mL, respectively). Lupus anticoagulant was negative. At the same time, she developed a reactivation of CMV infection with a viremia of 1,990 UI/mL that was successfully treated with valganciclovir. Due to the presence of antiphospholipid syndrome, we decided to carry on immunosuppressive therapy with rituximab (4 infusions of 375 mg/m^2/week) along with anticoagulation therapy.

During the hospitalization, respiratory symptoms progressively resolved and renal function gradually ameliorated. At discharge, the patient was in good clinical condition, and she was afebrile and did not complain of cough or dyspnea; her creatinine was 2.7 mg/dL.

Actually, 6 months after discharge, she is doing well, her serum creatinine is 2.03 mg/dL, proteinuria is 1.7 g a day, and no erythrocytes are present in the urinary sediment. PR3-ANCA, anticardiolipin, and anti-β2-glycoprotein-I antibodies are negative.

Discussion

Renal impairment is relatively common in patients affected by COVID-19 infection, especially in those with critical illness [2, 3]. Many studies from China, Europe, and the USA have reported a wide range of incidence of AKI, ranging between 1 and 50% [3]. In particular, a very recent study performed on hospitalized COVID-19 patients in New York City reports a burden of severe AKI with the need of renal replacement therapy (RRT) reaching almost 20% of the total cases. Importantly, AKI seems associated with lower patient survival, and the highest risk of death has been found in patients with AKI requiring dialysis. The same report

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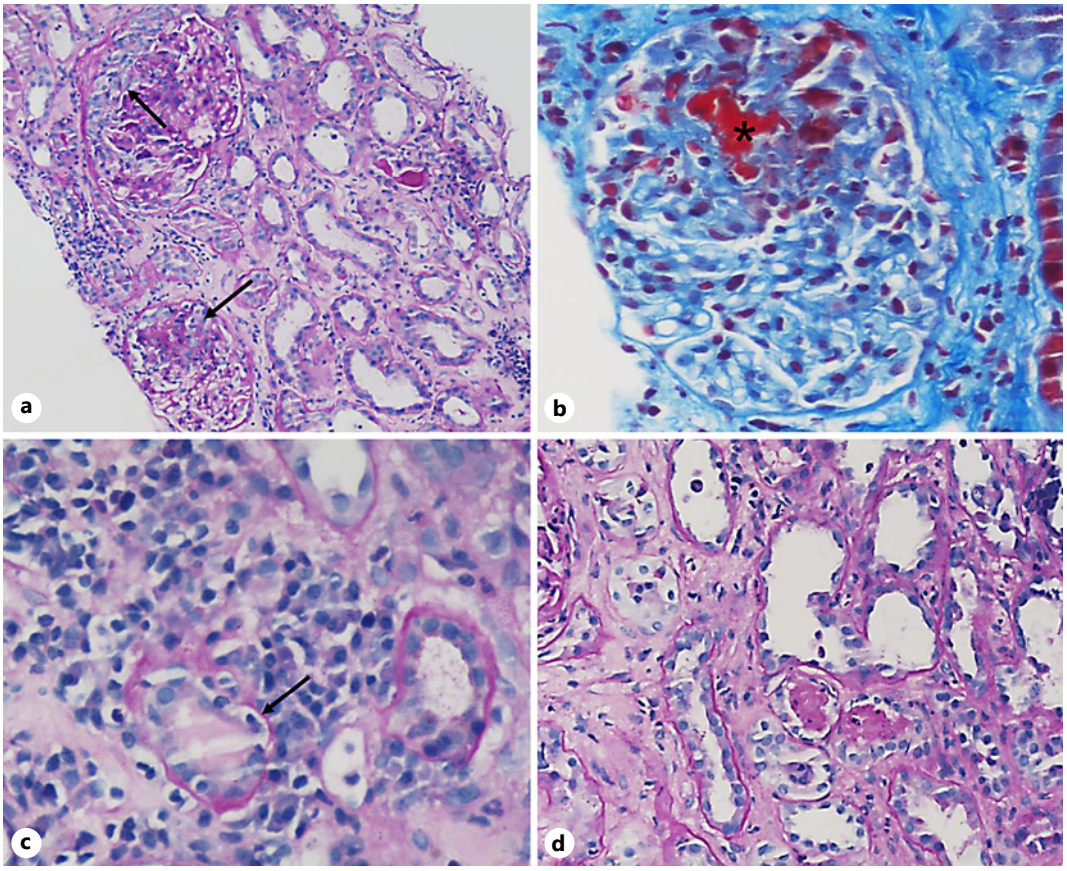

Fig. 1. Morphologic features of the kidney biopsy of a patient with acute kidney injury and COVID-19. **a** Glomeruli with cellular crescents (arrows) and sparse inflammatory infiltrate. **b** High magnification of a glomerulus with segmental fibrinoid necrosis (asterisk). **c** Tubular epithelium was infiltrated by mononuclear cells (arrow). **d** Cortex with acute tubular injury (PAS ×10 (**a**); PM ×20 (**b**); PAS ×20 (**c**); PAS ×20 (**d**)).

shows a persistence of kidney dysfunction even after discharge, with a third of COVID-19 patients who do not recover their baseline creatinine values [3].

The exact mechanisms of acute kidney damage in patients with SARS-CoV-2 infection are still unclear. Postmortem histological findings of patients with COVID-19 have revealed a prevalence of acute tubular injury. Although the same authors have postulated direct viral damage in the renal parenchyma by the finding of immunohistochemistry for the SARS-CoV-2 antigen nucleocapsid protein in epithelial cells [5], others deny this hypothesis, due to the lack of evidence of the virus in the renal tissue by the RT-PCR, and sustain that AKI results from hemodynamic instability [4]. On the other hand, different reports including black patients with APOL1 risk alleles developing AKI with proteinuria during SARS-CoV-2 infection have revealed that their renal biopsies show collapsing glomerulopathy without virus detection in the tissue, suggesting that SARS-CoV-2 infection may activate the systemic cytokine cascade and the adaptive or immune responses which may result in glomerular damage [7].

So far, pauci-immune glomerulonephritis in patients with COVID-19 is anecdotal. In a series of 10 kidney biopsies reported by Sharma et al. [6], one patient had pauci-immune crescentic glomerulonephritis. The case presented with AKI and nephrotic proteinuria and had anti-myeloperoxidase antibodies positivity. He started hemodialysis and received 3 pulses of

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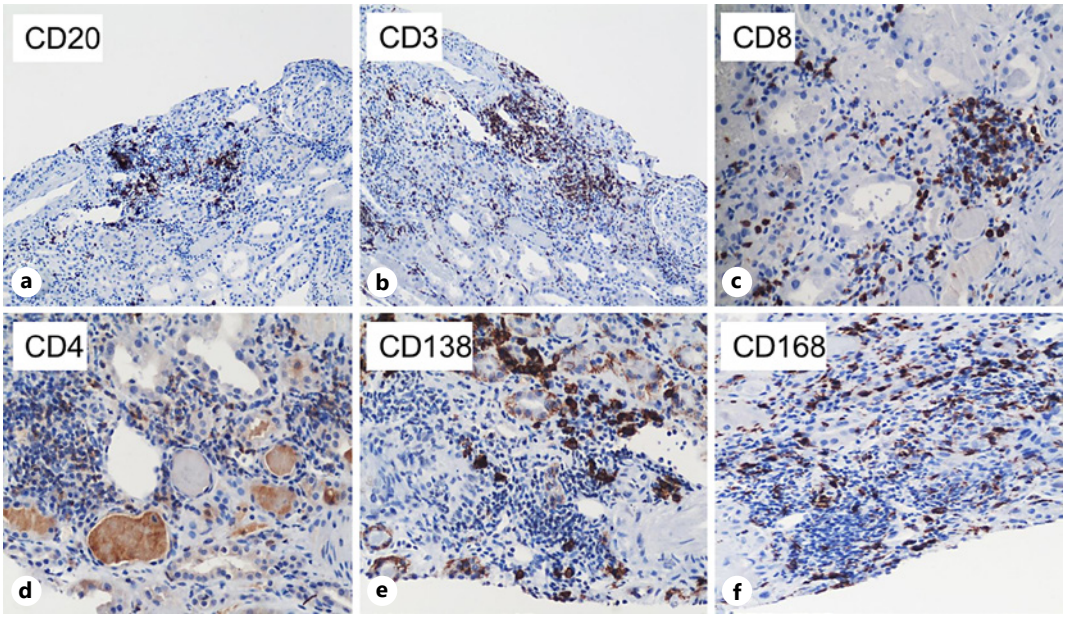

Fig. 2. Morphologic features of the kidney biopsy of a patient with acute kidney injury and COVID-19. Immunohistochemical staining of the interstitial inflammatory infiltrate was positive for markers of B lymphocytes (CD20), T lymphocytes (CD3, CD4, and CD8), plasma cells (CD138), and macrophages (CD68) (×10 (**a**, **b**); ×20 (**c–f**)).

methylprednisolone in addition to COVID-19 treatment including plasma therapy and tocilizumab, and was able to get out of dialysis. In May 2020, Moeinzadeh et al. [9] reported a case of crescentic glomerulonephritis in a patient with AKI and c-ANCA positivity and a concomitant nonsevere pneumonia due to SARS-CoV-2 infection. The patient was treated successfully with steroids and cyclophosphamide, together with hydroxychloroquine and antibiotics [9]. Finally, 2 cases of de novo ANCA-associated vasculitis with pauci-immune glomerulonephritis in COVID-19-positive patients have been reported in August 2020. One patient had an MPO-ANCA vasculitis and was treated with 3 pulses of methylprednisolone and with rituximab, once SARS-CoV-2 RT-PCR in nasal-pharyngeal swab becomes negative. The second patient, with a previous but recent diagnosis of pneumonia due to COVID-19, developed a PR3-ANCA necrotizing glomerulonephritis and was successfully treated with glucocorticoids and rituximab [8].

The cytokine storm has been also considered the cause of the increased thrombotic risk found in COVID-19 patients. Indeed, the host inflammatory response to SARS-CoV-2 may lead to a macrophage activation syndrome, which causes the activation of innate and adaptive immunity, platelet activation and coagulation, and complement cascades, and all of them may result in thrombosis. In this context, a role for lupus coagulants and antiphospholipid antibodies has also been considered, due to their high detection in these patients [10].

In this report, we have described a patient who developed an ANCA-associated glomerulonephritis and an antiphospholipid syndrome presumably more than one month after SARS-CoV-2 infection. Consistently with a recent SARS-CoV-2 infection, the serological test has shown a significant serum level of SARS-CoV-2 IgG and IgM [11]. Based on the absence of viral-RNA in the bronchoalveolar lavage, we hypothesized that the pulmonary findings could have been included as lung involvement in the course of vasculitis ANCA-associated, instead of COVID-19-associated, interstitial pneumonia. Nevertheless, the absence of alveolar hemorrhage raised the question if the interstitial pneumonia could be the result of a previous lung

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damage induced by SARS-CoV-2 infection and subsequently triggered by ANCA-associated vasculitis.

The mechanisms of the association between SARS-CoV-2 and ANCA-associated glomerulonephritis remain obscure. Nevertheless, it has been postulated that viral infection may influence innate or adaptive immune responses that, in turn, may trigger an autoimmune disease in specific predisposed hosts [8]. Indeed, ANCA-associated vasculitis develops by the loss of T-cell and B-cell tolerance to one of 2 neutrophil proteins, namely, PR3 or MPO. The loss of tolerance leads to the development of ANCAs that by activating neutrophils induce the injury in the microvascular bed. Infections may promote the loss of tolerance and autoantigen exposure by the formation of neutrophil extracellular traps (NETs) [12]. SARS-CoV-2 may induce a disproportionate NET release, which could play not only a key role in COVID-19 pathogenesis, but in the meantime, it could predispose to vasculitis [13]. NET formation unbalance has also been reported to be involved in antiphospholipid syndrome [12].

Consistent with the well-known impact of SARS-CoV-2 on the immunological system, we speculated that the recent SARS-CoV-2 infection may have triggered the development of the ANCA-associated vasculitis subsequently complicated by thrombosis due to antiphospholipid antibodies in our patient. Immunosuppression therapy during COVID-19 is still a matter of debate [14]. We reasoned that our patient had to be treated aggressively because of the presence of severe kidney involvement. We started treatment by using high doses of methylprednisolone and plasma exchange. Oral administration of cyclophosphamide was added only when SARS-CoV-2 was excluded in the bronchoalveolar lavage. Even if many authors advise not to use rituximab during the SARS-CoV-2 pandemic, we were forced to replace cyclophosphamide with rituximab when the patient developed thrombocytopenic due to antiphospholipid antibodies. Rituximab in fact has a less bone marrow toxicity than cyclophosphamide, and it has also been reported to be effective in patients with antiphospholipid syndrome [14, 15].

In conclusion, our case suggests the possibility that a previous infection with SARS-CoV-2 might induce an ANCA-associated vasculitis with kidney and lung involvement. The co-existence of anti-PR3 and antiphospholipid antibodies strengthens the hypothesis that the virus induces the activation of immune and inflammatory responses, which not only can lead to the severe manifestations of COVID-19 but also can favor systemic autoimmune diseases. Based on our experience, we suggest close monitoring of kidney function together with urinary signs related to glomerular involvement such as proteinuria and hematuria not only during COVID-19 infection but also after the end of viral infection in order to promptly diagnose and treat the onset of glomerulonephritis triggered by the dysregulation of the immunity status induced by SARS-CoV-2. At the same time, we suggest performing a serological test for SARS-CoV-2 in patients with AKI associated with urinary signs of active renal damage.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. (See included documentation.) The paper is exempt from ethical committee approval because it is not a research involving human subjects nor a clinical trial but a retrospective report of a single case report.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

F.M. conceived the report, interpreted results, and wrote the manuscript; M.I.M., V.N., S.R., P.G., M.T., and W.B. contributed to the interpretation of the data; R.M. and M.M. performed histopathologic evaluation and contributed to the interpretation of the data; P.B. contributed to the virologic data; A.R. conceived the report, interpreted results, provided intellectual content of critical importance, revised the manuscript, and approved the final version.

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